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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,889	01/19/2001	Rosalie Luiten	L0461/7104	9782

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John R. Van Amsterdam
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,889	LUITEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/27/01, 8/9/02, 5/12/03, 9/2/03, 2/12/02, 1/20/04 & 6/7/04.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 8,9 and 79-85 is/are pending in the application.

4a) Of the above claim(s) 9 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8 and 79-85 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date attached hereto.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 7/27/01, 8/9/02, 5/12/03, 9/2/03 and Applicant's responses filed 2/12/02, 1/20/04 and 6/7/04 are acknowledged and have been entered.

2. Applicant's election without traverse of Group I (claims 8 and 79-85) in Applicant's response filed 6/7/04 is acknowledged.

Accordingly, claim 9 (non-elected Group II) is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, and claims 8 and 79-85 are currently being examined only to the extent that they read upon the method for stimulating an immune response in an HLA-B35 positive subject comprising administering a MAGE-A1 HLA-B35 binding peptide comprising SEQ ID NO: 10 (ADPTGHSY).

3. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figures 3, 7 and 11).

4. The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 21 at lines 6 and 7 and on page 52 at line 9. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 8 and 79-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant

had possession at the time of invention of the claimed method for stimulating an immune response comprising administering a functional variant of SEQ ID NO: 8, 9 or 10, nor comprising administering an HLA-B35 binding peptide comprising SEQ ID NO: 10 that is not SEQ ID NO: 8 or 9, nor one comprising SEQ ID NO: 8, 9 or 10 that is not a fragment of SEQ ID NO: 2.

The instant claims encompass a method of using functional variants of SEQ ID NO: 8, 9 or 10 that are not substitution variants of the said SEQ ID NO and/or that may bind HLA-B35, but not stimulate T cells, i.e., the peptide may be up to any length for binding HLA-B35, it may have any combination of amino acid residues as long as it binds to HLA-B35. There is insufficient disclosure in the specification on making such a functional variant and using it in the claimed method.

The specification discloses that methods for identifying functional variants of a MAGE-A1 HLA-B35 binding peptide *include* providing a MAGE-A1 HLA-B35 binding peptide, an HLA-B35 molecule and a T cell specific for/restricted by the said peptide/HLA combination The specification further discloses that the methods also include mutating a first amino acid residue of the said peptide to prepare a variant peptide, and determining the binding of the variant peptide to HLA-B35 *or* stimulation of the T cell by the variant peptide presented by HLA-B35.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any lipid or portion thereof. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

7. Claims 79 and 80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and use the instant invention, of the claimed method for stimulating an immune response comprising administering a functional variant of SEQ ID NO: 8, 9 or 10.

The specification has not enabled the breadth of the claimed invention because the claims encompass a method of using functional variants of SEQ ID NO: 8, 9 or 10 that are not substitution variants of the said SEQ ID NO and/or that may or may not bind HLA-B35, and may or may not stimulate T cells, i.e., it may have any combination of amino acid residues as long as it binds to HLA-B35. A nonamer peptide would have 9^{20} possible permutations, according to 20 potential amino acid residues at each position.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed functional variant can be made and used in the claimed method. The specification discloses that methods for identifying functional variants of a MAGE-A1 HLA-B35 binding peptide *include* providing a MAGE-A1 HLA-B35 binding peptide, an HLA-B35 molecule and a T cell specific for/restricted by the said peptide/HLA combination respectively. The specification further discloses that the methods also include mutating a first amino acid residue of the said peptide to prepare a variant peptide, and determining the binding of the variant peptide to HLA-B35 *or* stimulation of the T cell by the variant peptide presented by HLA-B35.

The specification discloses no working examples of functional variants that are not peptides comprising SEQ ID NO: 10 with flanking amino acid residues from SEQ ID NO: 2.

Evidentiary reference Celis et al (Molecular Immunol. 3: 1423-1430, 1994) teach that although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA and inducing a CTL response. Kast et al (Eur. J. Immunology 1993, 23 1189-1192) teach that the amino acid residues can exert important effects upon the binding capacity of a peptide. DiBrino et al (J. Immunology 151(11) 5390-5935, 1993) teach that the presence of anchor residues is not sufficient for binding to HLA because peptides with optimal amino acid residues at anchor positions failed to bind. Karin et al (J. Exp. Med. 180: 2227-2237, 1994) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. Karin et al teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin et al establish that amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides are immunogenic. Anderton (Immunology 2001 104 367-376) teaches that in vivo use of altered peptide ligands is unpredictable and dangerous in outbred human populations (especially paragraph spanning columns 1 and 2 on page 370).

In addition, although the specification discloses on pages 52-53 and in Figure 3 that an 8-mer peptide consisting of SEQ ID NO: 10 (ADPTGHSY) was recognized but less efficiently than SEQ IDNO: 8 (a 9-mer) and SEQ ID NO: 9 (a 10-mer), the art (Rammensee et al Immunogenetics, 1995) recognizes that HLA-B35 binds to peptides that are at least 9-mers. The art further recognizes that the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino

acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends." (Engelhard at page 14, column 1, lines 23-27). The minimum amount of peptide required to span the binding groove and make favorable contacts with their N-and C-termini may be dependent upon the sequence of the peptide itself since different amino acid residues have different physicochemical properties, and may be dependent upon the identity of the additional amino acids, since these residues may make a negative contribution to binding.

Accordingly, there is a high level of unpredictability in designing/selecting 8-mer sequences that are not identical to SEQ ID NO: 10 that would still maintain binding function and be immunogenic, or in predicting which 9-mer peptides and longer would bind to HLA-B35 and stimulate a T cell presenting some MAGE-1 HLA-B35 binding peptide and to use it in the claimed method, and Applicant does not provide direction or guidance to do so.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 80 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 80 recites the limitation "(ii) functional variants of the peptides of (i)" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim because base claim 8 does not recite the linitation "(i)" or "(ii)".

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 8 and 79-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,667,037 B1 in view of WO 95/04542, Rammensee et al (Immunogenetics, 1995, 41: 178-228, IDS reference), Rammensee et al (MHC Ligands and Peptide Motifs, 1997, pages 263-265) and admitted prior art in the specification on pages 62-63 at the sentence spanning the said pages.

U.S. Patent No. 6,667,037 B1 discloses the MAGE-1 antigenic peptide EADPTGHSY (SEQ ID NO: 8 of the instant claims and an HLA-B35 binding peptide comprising SEQ ID NO: 10 of the instant claims) restricted by HLA-A1 and testing of complexes of HLA/β2m in combination with this peptide for identification or isolation of CTL (especially Column 6 at line 26). U.S. Patent No. 6,667,037 B1 further discloses peptides (TAAs, tumor rejection antigens) that bind to HLA-B35 from the melanoma TRAP tyrosinase can be administered to HLA-B35 positive patients to induce a CTL response, and further that they can be administered in combination together, or as polytope constructs along with peptides from other TRAPs and with MHC class II restricted peptides, i.e., Th epitopes, and the compositions may include adjuvants such as the cytokines IL-6 or IL-12 (especially abstract, paragraph spanning columns 4 and 5, sentence spanning columns 6 and 7, columns 7 and 8).

U.S. Patent No. 6,667,037 B1 does not disclose wherein the TAAs from tyrosinase are administered along with EADPTGHSY in a composition that includes cytokines.

WO 95/04542 teaches that MAGE-1 is a melanoma TRAP that contains TAA peptides that can be combined in a cocktail to provide enhanced immunogenicity for CTL or Th-mediated responses and administered to patients, and that the cocktail may include universal Th epitopes (especially page 12, Abstract). WO 95/04542 teaches that the peptides of one region of a TRAP can be combined with peptides having different MHC restriction elements in order to effectively broaden the immunological coverage provided by therapeutic, vaccine or diagnostic compositions among a diverse population, and that HLA-A1 binding peptides are useful in such compositions (especially page 12 at lines 5-23).

Rammensee et al (Immunogenetics) teach that the motif for peptides that bind to HLA-B3501 is P2 proline and P9 tyrosine, whereas the motif for peptides that bind to HLA-A1 is D or E at position 3 and Y at P9, i.e., that the peptides that bind to each have a common P9 anchor residue. Rammensee et al further teach preferred residues at non-anchor positions. Rammensee et al further teach the peptide EADPTGHSY is a T cell epitope from MAGE-1 that binds to HLA-A1.

Rammensee et al (MHC Ligands and Peptide Motifs) teach that preferred residues for peptides that bind to HLA-B3501 include A at the P2 anchor position, and P at the P4 and T at the P5 non-anchor positions (as does EADPTGHSY) and that a T cell epitope peptide (TAVPWNASW) containing no primary anchor residue amino acid residues, has the preferred residues A at the P2 anchor position, P at the P4 non-anchor position and S at the P8 non-

anchor position (as does E**A**D**P**TGH**S**Y) is a T cell epitope from HIV env protein (pages 263-265).

The admitted prior art in the specification on pages 62-63 at the sentence spanning the said pages is that Pagupathi et al teach that at least 27 different HLA-B35 alleles have been identified and that HLA-B3501, and HLA-B3503 have 12% frequency.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MAGE-1 antigenic peptide EADPTGHSY restricted by HLA-A1 disclosed by U.S. Patent No. 6,667,037 B1 and by Rammensee et al in the composition of U.S. Patent No. 6,667,037 B1 with the HLA-B35 binding peptide(s) disclosed by U.S. Patent No. 6,667,037 B1 since WO 95/04542 teaches that the peptides of one region of a TRAP can be combined with peptides having different MHC restriction elements in order to effectively broaden the immunological coverage provided by therapeutic, vaccine or diagnostic compositions among a diverse population, and that HLA-A1 binding peptides are useful in such compositions and Rammensee et al teach anchor residues for peptides that bind to both HLA molecules and the admitted prior art is that HLA-B35 alleles have a high frequency in the population, as does HLA-A1, as was recognized by one of skill in the art at the time the invention was made. It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MAGE-1 antigenic peptide EADPTGHSY restricted by HLA-A1 disclosed by U.S. Patent No. 6,667,037 B1 and Rammensee et al in the composition of U.S. Patent No. 6,667,037 B1 with the HLA-B35 binding peptide(s) disclosed by U.S. Patent No. 6,667,037 B1 because one of ordinary skill in the art at the time the invention was made would have realized that the MAGE-1 peptide might also bind to HLA-B53 since Rammensee et al (both references) teach anchor residue and preferred residue motifs for peptides that bind to HLA-A1 and to HLA-B35 include a common P9 anchor residue of "Y" as does EADPTGHSY, and since Rammensee et al (MHC Ligands and Peptide Motifs) teach that E**A**D**P**TGH**S**Y has preferred residues at the anchor and non-anchor positions (bolded and underlined) and that an antigenic peptide that binds to HLA-B35 lacked optimal anchor residue amino acids or had non-preferred amino acid residues at the anchor positions, but had preferred amino acid residues at anchor or non-anchor positions.

One of ordinary skill in the art would have been motivated to do this in order to make a composition comprising HLA-B35 and HLA-A1 binding antigenic peptides for use in a therapeutic composition such as that taught by U.S. Patent No. 6,667,037 B1 and by WO 95/04542 to provide coverage of more than one frequent MHC class I allele in a diverse population for more than one melanoma specific antigen, i.e., tyrosinase and MAGE-1 using peptides taught by U.S. Patent No. 6,667,037 B1 and Rammensee et al, that diverse population including an individual possessing HLA-B35.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
September 29, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600